Al-Azhar Bulletin of Science

Volume 20 | Issue 2 Article 5

12-1-2009
Section: Botany, Microbiology and Zoology

IMMUNE INDUCTION BY NATURAL PRODUCT AND PIPERAZINE CITRATE DRUG IN RATS INFECTED WITH ASCARIS LUMBRICOIDES

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IMMUNE INDUCTION BY NATURAL PRODUCT AND PIPERAZINE CITRATE DRUG IN RATS INFECTED WITH *ASCARIS LUMBRICOIDES*

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Abstract

Ascaris lumbricoides remains the most common intestinal nematode in the world. The cytokine are considered the arm of the adaptive immune system is mediated by T helper cells (Th1and Th2) and related cytokines, including interferon (IFN)-γ and tumor necrosis factor (TNF)-α, and has been reported to play a pivotal role in the control of many parasites . This study investigates the antihelmintic effect of natural product (Allicin garlic) extracts and also synthetic drugs (Piperazine Citrate). Our target was to study the effect of natural and synthetic drugs on immune induction of infected rats by *Ascaris lumbricoides* . Ninety male rats *Rattus Rattus* were used. The rats were divided into 7 groups. The 1st group was control clean, and the second group was infected control . The groups (3, 4, 5,and 6) were treated by Allicin garlic extracts i.m 8 times twice weekly at 0.1, 0.2 , 0.3 and 0.4 mg/kg respectively). The Seventh group received Piperazine Citrate drug at dose 10 mg/kg body weight 8 times twice weekly. All groups were scarified after 30 days and investigated with the immunoresponse (cytokine) IL-10 and TNF – alpha, paralleled with measurements the ALT, AST, ALP, GGT and Malondialdehyde as an immune factor . The results of the current study revealed that the levels of IL-10 and TNF- alpha were increased significantly in groups treated with natural product (Allicin garlic) . also our data reveled that the MDA level was decreased significantly in groups treated with natural product (Allicin garlic) . On the other hand liver function ALT , AST , ALP and GGT were reveled the significant increased in groups treated by natural product (Allicin garlic as well as Piperazine Citrate drug .

Key words *: MDA- IL-10- TNF- alpha- Allicin - Piperazine Citrate*

Introduction

Ascaris lumbricoides is one of the most frequent metazoan parasite of humans, and ascaridiasis is currently estimated to reach a prevalence of 1.472 billion of cases worldwide **(Busse and Lemanske, 2008),** especially in moist, tropical, and subtropical regions but also in cooler climates. Although characterized by low morbidity and mortality rates, the global prevalence of ascaridiasis still results in approximately 20, 000 deaths yearly. In humans, transmission usually occurs by hand-to-mouth route by way of contaminated agricultural products and food or from dirty hands **(Larche and Robinson 2007).** Atopic diseases are mediated by T helper type 2 (Th2) cells releasing some cytokines, especially interleukin (IL)-10 and (IFN)-γ, associated with elevated tumor necrosis factor (TNF)-α, responses to common allergens and eosinophilia **(Larche and Robinson 2007).** Such a

pathogenic cascade is very similar to the adaptive immune response to helminthes. The other arm of the adaptive immune system is mediated by T helper type 1 cells (Th1) and related cytokines, including interferon (IFN)-γ and tumor necrosis factor (TNF)-α, and has been reported to play a pivotal role in the control of many viral, bacterial, and protozoan infections **(Daser *et al*., 2009).**

Control of ascaridiasis can be achieved through chemotherapy by Piperazine Citrate and natural product allicin extract . Allicin is formed by the action of alliin-lyase on alliin(S-allyl-L-cysteine sulphoxide). Enzyme and substrate become mixed on mechanical damage to the cells and the typical odour of garlic that results is attributable to allicin production The reaction proceeds rapidly and conversion is approximately 97% complete after 30 s at 23 8C . Thus, allicin can be viewed as a phytoanticipin rather than a phytoalexin **(Hlaingand and Lwin, 2008).**

Properties of plant essential oils on Control of ascaridiasis some plant oils have immunomodulatory effects that are useful for treating infectious diseases, particularly in cases where the oil has no direct adverse effect on the host. turmeric and garlic oils inhibit nitric oxide (MDA) production in macrophages. MDA is a potent intracellular parasite-killing mechanism in macrophages and macrophages are pivotal in the innate immune response **(Shepherd and Wenk, 2006) .**

Piperazine is a bulk product in organic synthesis. It is made from ethanolamine by heating it in ammonia at a temperature of 150–220C and a pressure of 100–250 atm. It is used as a drug in the form of a salt, and as a rule, in the form of adipinate **(Mauro and Macedo , 2005).** Piperazine is an alternative drug and is used for treatment of various forms of nematodes, in particular for enterobiasis and ascariasis. It causes paralysis in the nematode by blocking acetylcholine transmission. This causes the parasite to detach from the mucous membrane, where it is removed from the body. Ascariasis requires treatment for 2 days, and enterobiasis, for 7 days **(Mauro and Macedo , 2005).**

Material and Methods:

I- Experimental animals:

Ninety male rats (*Rattus rattus)*, aged 2-3 months (100-110 g), and were used in the present study. Mice were obtained from **Biological supply Unit (SBSU) at Theodor Bilharz Research Institute, Cario, Egypt**. Rats were kept in cages under hygienic conditions, fed on standard rodents chow and supplied with water. The eggs of *Ascaris lumbricoides* were obtained from **Biological supply Unit (SBSU)**

at Theodor Bilharz Research Institute, Cario, Egypt. The infective *Ascaris lumbricoides* eggs were introduced directly into the stomach of rats by use of oral gavage tube.

2- Chemotherapy: Piperazine Citrate (Citric acid sesquipiperazine salt) obtained from (Nile Pharmaceutical Company Cairo, Egypt). in a form of capsule, chemical formula $C_6H_8O_7 \cdot 1.5C_4H_{10}N_2$.

3- Preparation of natural product (garlic – **allicin** extract) 2-propene-1-sulfinothioic acid S- , chemical formula $C_6H_{10}OS_2$ extracted from the plant Allium sativum. it was extracted with light petroleum ether according to (Timmermann , 2005). The extracts were concentrated and evaporated from traces of water under rotator evaporator apparatus and were kept at a temperature not exceeding 45°C until used .

4-Animal infection model and treated groups :

All experimental groups were infected with infective *Ascaris lumbricoides* eggs the protocol of treatments was started after 15 days from the first infection The first group of rats was infected control. The second, third, fourth, and fifth groups were treated by natural product (garlic extract (Allicin) intramuscular at a dose 0.1, 0.2, 0.3, 0.4 mg /kg body weight 8 times twice weekly respectively. The 7 group were treated by anthelminthic drug (Piperazine Citrate) orally at a dose 10 mg /kg body weight 8 times twice weekly.

:Biochemical study

1- **Plasma alkaline phosphatase activity was determined according to method of** (Szaz and Kindrhelik 1971&Klin 1972).

2- **AST and ALT** determination **was according to the method adopted by** Henry and Frankle 1960).

3- Gamma Glutamyltransferase (γ - GT) **was determined according to** Szaz and Tiets (1969).

4- Malondialdehyde (MDA) determination **was according to the method adopted by** (Yagi, 1998 and Armstrong & Browne , 1994).

5- Measurements of Cytokine IL-10 was described by Mosmann,1994 and Defu,1998).

6- Measurements of Cytokine TNF – alapha according to Thomas ,1994 and Friedman, 1997).

Results

Evaluation of ALP (Table 1) demonstrates the effect of Piperazine Citrate and natural garlic extract on ALP in rats infected with *Ascaris lumbricoides* The results in table (1) indicate that ALP levels were significantly increased in garlic extract (0.2mg/kg allicin) and Piperazine Citrate groups amounted 77.1, 76.8% respectively in comparison to control. Also infected control reveled increased in percent reached up to 221.2 % in compared to control group .

Evaluation of Aminotransferases: (Table 2) demonstrates the effect of Piperazine Citrate and natural garlic extract on AST and ALT in patients infected with *Ascaris lumbricoides* The data obtained in table 2 indicated that AST levels were significantly decreased in (0.2 and 0.4 mg/kg natural garlic extract) groups reaching 69.1and 63.5 % respectively in comparison to control group. The more pronounced increase was observed in the Piperazine Citrate group reaching 155.8 % as compared to control group. The data also revealed highly significant increase in the ALT level in (0.1, 0.2 mg/kg and Piperazine Citrate) groups reached 122.5, 98.5 and 135.5 % respectively with respect to control group. It is worthy to mention that ALT levels were relatively decreased in the (0.2 and 0.4 mg/kg groups) $P < 0.001$ as compared to the infected control group.

Evaluation of γ – GT

(Table 3) demonstrates the effect of Piperazine Citrate and natural garlic extract on γ – GT in patients infected with *Ascaris lumbricoides* The data obtained revealed a higher significant increase in serum γ – GT levels in the (0.1,0.3 mg/kg and Piperazine Citrate) groups amounted 69.4,94.5 and126.2% respectively as compared to control group.

Evaluation of Malondialdehyde (MDA) (Table 4) demonstrates the effect of Piperazine Citrate and natural garlic extract on MDA in rats infected with *Ascaris lumbricoides* A significant increase was recorded in serum MDA levels in the (0.1, 0.2, 0.3 mg/kg and Piperazine Citrate) groups amounted 275 , 178.2 and 212.5 % respectively as compared to control group.

Evaluation of Cytokine (IL-10)

(Table 5) demonstrates the effect of Piperazine Citrate and natural garlic extract on IL-10 in patients infected with Ascaris *lumbricoides*. A significant increase was recorded in serum IL-10 levels in the (0.1,0.2 ,0.3 , 0.4 mg/kg and Piperazine Citrate) groups amounted 108.2 , 89.9 , 112.6 , 120.8 and 99.1 % respectively as compared to control group.

Evaluation of Cytokine (TNF- alpha)

(Table 6) demonstrates the effect of Piperazine Citrate and natural garlic extract on TNF- alpha in patients infected with *Ascaris lumbricoides* A significant increase was recorded in serum TNF- alpha level in the (0.1,0.2 ,0.3, 0.4 mg/kg and Piperazine Citrate) groups amounted 118.6, 128.1, 106.2 ,130.6 and 96.1 % respectively at p<0 .001 as compared to control group.

Table (1): Effect of Piperazine Citrate and natural garlic extract on ALP rats infected with *Ascaris lumbricoides*

Group / Item	control	Infected control	Allicin 0.1mg/kg	Allicin 0.2 mg/kg	Allicin 0.3 mg/kg	Allicin 0.4 mg/kg	Piperazine Citrate
	SE Mean±	SE Mean±	SE Mean±	SE Mean±	SE Mean±	Mean±SE	SE Mean±
ALP U/L	35.47± 1.2 100%	78.52±0.8 *** 221.2%	±01.1 32.78 NS 41.7%	±0.9 55.89 *** 71.1%	±0.8 45.68 ** 58.1%	±1.3 40.73 ** 51.8%	±1.0 60.34 *** 76.8%

Table (2) : Effect of Piperazine Citrate and natural garlic extract on Aminotransferases in rats infected with Ascaris lumbricoides

Group / Item	control	Infected control	Allicin 0.1 mg/kg	Allicin 0.2 mg/kg	Allicin 0.3 mg/kg	Allicin 0.4 mg/kg	Piperazine Citrate
	SE Mean±	SE Mean±	SE Mean±	SE Mean±	SE Mean±	Mean±SE	SE Mean±
AST U/L	31.25±0.9 100%	48.45±0.8 *** 155.1%	41.76±1.1 * 86.1%	33.47±0.9 ** 69.1%	46.33±0.7 ** 95.6%	30.54±0.5 *** 63.5%	47.36±1.2 *** 155.8%
ALT U/L	27.63± 0.7 % 100	37.52±0.3 *** 135.7%	45.97±1.1 ** 122.5%	36.87±2.1 *** 98.5%	23.51±2.3 *** 62.5%	30.05±2.0 ** 80.5%	50.76±3.2 *** 135.5%

Table (3) : Effect of Piperazine Citrate and natural garlic extract on γ – GT in rats infected with Ascaris lumbricoides

Group Item	control	Infected control	Allicin 0.1mg/kg	Allicin 0.2 mg/kg	Allicin 0.3 mg/kg	Allicin 0.4 mg/kg	Piperazine Citrate
	SE Mean±	SE Mean±	SE Mean±	SE Mean±	SE Mean±	Mean±SE	SE Mean±
γ – GT U/L	7.87± 0.9 100%	12.66±0.6 *** 160.82%	±0.3 8.78 *** 69.4%	13.48±0.7 ** 106.5%	11.95±0.8 *** 94.5%	10.5±0.4 * 82.6%	11.6±0.2 ** 126.2%

Table (4): Effect of Piperazine Citrate and natural garlic extract on Malondialdehyde in rats infected with Ascaris lumbricoides

Group Item	control	Infected control	Allicin 0.1mg/kg	Allicin 0.2 mg/kg	Allicin 0.3 mg/kg	Allicin 0.4 mg/kg	Piperazine Citrate
	SE Mean±	SE Mean±	SE Mean±	SE Mean±	SE Mean±	Mean±SE	SE Mean±
MDA	0.18±0.12 100%	0.32±0.1 *** % 177.76	±0.17 0.88 *** 275%	0.72±0.14 *** 225%	0.57±0.12 *** 178.2%	0.38±0.16 * 118.7%	0.68±0.18 ** 212.5%

Table (5): Effect of Piperazine Citrate and natural garlic extract on IL-10 in rats infected with Ascaris lumbricoides

Group Item	control	Infected control	Allicin 0.1mg/kg	Allicin 0.2 mg/kg	Allicin 0.3 mg/kg	Allicin 0.4 mg/kg	Piperazine Citrate
	SE Mean±	SE Mean±	SE Mean±	SE Mean±	SE Mean±	Mean±SE	SE Mean±
IL-10 (pg/ml)	335.88± 5.2 100%	550.72±8.7 *** % 163.96	±9.4 595.68 *** 108.2%	495.52±5.8 *** 89.9%	620.55±9.5 *** 112.6%	665.66±8.9 *** 120.8%	545.85±7.3 ** 99.1%

Table (6): Effect of Piperazine Citrate and natural garlic extract on TNF – alapha in rats infected with Ascaris lumbricoides

Group Item	control	Infected control	Allicin 0.1mg/kg	Allicin 0.2 mg/kg	Allicin 0.3 mg/kg	Allicin 0.4 mg/kg	Piperazine Citrate
	SE Mean±	SE Mean±	SE Mean±	SE Mean±	SE Mean±	Mean±SE	SE Mean±
TNF – alapha (pg/ml)	220.63±2.4 100%	310.74±3.4 *** % 140.84	±4.8 368.68 *** 118.6%	398.36±4.1 *** 128.1%	320.25±3.7 *** 106.2%	405.89±5.6 *** 130.6%	298.77±3.9 ** 96.1%

Significant difference from infected group P < 0.05 *
Significant difference from infected group P < 0.01 **
Significant difference from infected group P <0 .001 ***

Discussion

The aim of the current study is to compare between the efficacy of chemotherapy and natural products in treatment of *Ascaris lumbricoides* infection.

Our data obtained showed significant increases in ALP (alkaline phosphatase) (P <0 .001) in all of the studied groups as well as elevation in the serum activity of ALT, ɣ-GT. This results confirmed by **Lorcain (2000)** who observed that an elevation in ALP activity in liver after *Ascaris lumbricoides* infection.

Vincent, (2005) showed an increase in ALP enzyme activity in infection with *Ascaris* and attributed it to the proliferation of bile ductless and bile canaliculi. In concerning to the study of transaminases enzyme activities, which showed a significant increase after infection, **Wright and Bickle (2005)** attributed the increase of transaminase enzyme activities in rat livers to the decrease in hepatic cell population due to liver fibrosis or due to the release of the enzyme from the damaged livers into the circulation as a result of increased cell membrane permeability. The observed diminution of AST was more manifested than that of ALT denoting that, although the later is more specific for liver cells, yet it is less sensitive than AST in detecting liver cell damage. **Finnen *et al.*, 2008** reported that is the presence of considerably more AST in human hepatic tissue indicated that the released ALT is too diluted in the extracellular compartment to cause significant increase in the ALT activity in *Ascaris lumbricoides* rats . Therefore, variations in the release, destruction or excretion of the two enzymes or an unknown metabolism aberration are probably important contributory mechanisms **(Wright and Bickle , 2005**).

Homogenate prior to challenge infection partially ameliorated some serum ɣ-GT, ALT, as well as reduction in morbidity. These results are in agreement with **Enobe, C.S. (2006)** who suggested that increased transaminase activity in mice immunized by schistosomules homogenate, also activity of AST in with either Piperazine Citrate or natural garlic extract allicin is less than activity of ALT because ALT is more sensitive in both acute and obstructive liver disease while AST is more sensitive in most chronic and infiltrative lesions .

In view of the data obtained in the present study showed a highly significance increase in serum ALT and AST of rat infected by Ascaris reaching 135.7%. , 155.1%, these changes could be attributed to the hepatocellular injury, which in turn lead to release of the enzymes from the hepatic cells into the blood stream; this

explanation was confirmed by Guevara *et al*., (2008) they attributed the changes in transaminases to persistent acute hepatic cell damage and / or increased membrane permeability of the cells. Also, the increase in serum ALT was reported to be specific for necrosis and liver damage as described by Else *et al* ., (2007) .

Our data showed increase in the TNF-α and IL-10 cytokines as the result of enhanced immune response against parasites in infected rats**,** this confirmed by **Macedo, (2007)** who stated that the enhanced immune response due to increased TNF- α production. The TNF- α are likely candidates given their enhanced expression in IL-10 in infected rats with *Ascaris* , and play an important role in the immune response.

In the current study IL-10 revealed markedly elevation in infected rats , the elevation of serum IL-10 attributed to increased significantly in TNF – α level, such results is in agreement with **Geyer ,(2006)** who found that IL-10 in large part responsible for the suppression of TNF- α expression in infected mice. These findings were also agree with **Faquim, (2007)** who stated that the early Th1-type response is an essential component of the immune induction , and that immune modulation occurs as a result of the down-regulation of the Th1 response**.**

Also the results from this study suggest a plausible role for natural product to induced the IL-10 in the host immune regulation, so the significant increase was recorded in rats treated by allicin garlic extract at dose 0.1, 0.2, 0.3 and 0.4 mg/kg $p<0.001$, also infected group recorded highly significant increased in IL-10 level $p<0.001$ as compared to control group. This data was confirmed by **Matthale, 2007** who observed the requirement for IL-10 is critical in several important human diseases including Ascaris where in marked increases in host morbidity and mortality**.** IL-10 reduces damage induced by the Ascaris eggs and is essential for maintaining a non lethal chronic infection **(Guerra, 2004).** IL-10 is produced by a variety of cells following infection, including activated T cells and macrophages **(Macedo, 2009).**

One of the many essential functions of IL-10 during an immune response is to regulate the development of the CD4 and T cell response. Several cytokine blocking and gene knockout studies showed that IL-10 is in large part responsible for the establishment of the polarized Th2 response that characterizes helminth infections

(Lucius and Trees 2002). The Th2-associated cytokines IL-4, IL-5, TNF- α and IL-10 all play important roles in the pathogenesis of Ascariasis **(Rolfe and Sato, 2003).**

The role of IL-10 is a key agent in the control of excessive inflammation and immune-related immunopathologies. In this study, we show that the production of IL-10 in rats treated by natural product (allicin) has an important role in controlling mediated immune events that in turn govern the scale of the Th1 and Th2 type protective immune response.

Beyond the stage of infection, IL-10 plays a more important role in this stage, although improved, prolonged, or more targeted delivery of IL-10 by regulatory T cells at the site of immune induction might play a role of regulatory the Th2 cytokines **(Maizels, and Denham, 2007).** It has been proposed that IL-10 is a key player in the polarization of both T1 and T2 responses in immune response studies **(Berry and Fathman, 2007).**

Our results also showed highly significant increased in TNF- α ($p<0.001$) in rats treated by natural product (allicin) such results is in agreement with **Daser *et al.* ,(2009)** they found that TNF- α was significantly increased in rats treated by natural product, Th2- associated cytokines were only partially and variably decreased, IL10 showed also a sustained polarization in the Th1 direction and showed no significant increase in Th2-type cytokine expression.

Our result demonstrate that, while IL-10 essential for immune down-modulation in Ascariasis, the cytokine has an important role in regulating early acute disease as well as the character of the developing immune response ,this result coincide with **Daser *et al.* ,(2009)** they suggested that TNF-α production was also augmented by IL-10 levels were although response is necessary for regulating and appears to play an essential host-protective role in Ascariasis **.**

In the present study Piperazine Citrate treatment showed a higher increased levels of liver function as ALT , ALP , AST and ɣ-GT ($p<0.001$) this data parallel with increased in MDA reached (212.5%) in comparison to the control group. Also in this study TNF-alpha revealed that rats treatment with Piperazine Citrate 10 mg/kg body weight showed a higher significant reached (96.1%) at ($p<0.001$), this data coincide with **Finnen et al., (2009)** who explained the high effect of Piperazine Citrate on liver enzyme , and reduction on worm burden and oogram

stages. The rats infected for 10 days with 200 Ascaris eggs and treated with Piperazine Citrate (25 mg/kg subcutaneously) have more efficient acquired immunity and moderate immune response. Such results are in full agreement with **Matthale, (2007)** who detected Piperazine Citrate when given two weeks post levamisole treatment and with the challenge infection increased the percent resistance to 80%. The increase in percent resistance recorded in rats receiving both Piperazine Citrate and levamisole was accompanied by induction for immune response Th1 and Th2 .

Our results reveals beside efficacy of natural product as immunoregulant in Ascariasis possible role for the regulating immune response as a T-cell mediated response in maintenance of immunity in patients infected by Ascaris , similar results were reported by **Guerra, (2004)** who showed that the natural product inhibited circulating eosinophils and eosinophil activation when given alone, but caused immune stimulation when combined with praziquantel. The exact mechanism of action still needs to be determined .

Our results are consistent with previous studies have suggested an association between helminthiasis and an increased MDA in ascariasis. The present study was suggested that ascariasis may act to potentiate the MDA which play a role for mediated immune response and characteristic immune response in state of infection, similar results were reported by **Sack, (2006)** who showed the relationship between helminthiasis infection levels of MDA which can cause serious pathology and oxidative stress mechanism as a mediator of tissue damage concurrent on body worm of Ascaris .

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المخلص العربي

الحث المناعي بإستخدام مستخلص طبيعي مع عقار سترات الببرازين في الفئران المصابة بالإسكارس

أدهم جمال صادق
قسم علم الحيوان - كلية العلوم – جامعة الأزهر

الاسكارس لا تزال الديدان المعوية الاكثر شيوعاً في العالم .
السيتوكينات تعتبر الذراع الموائمة للنظام المناعي بواسطة خلايا تي 1 و 2 المساعدة والمرتبطة ايضا بانتاج السيتوكين والتي تشمل الجاما انترفيرون وتي – ان –اف – الفا والانترلوكين -10 وهذه تلعب دورا حيويا في التحكم في العدوي عديد من الطفيليات ومنها الاسكارس ، هذه الدراسة تبحث في تأثير مضادات الديدان واستخدام مستخلص طبيعي وهو مستخلص الالسين من نبات الثوم وايضا مع دراسة تأثير عقار مخلق هو سترات الببرازين علي الحث المناعي للفئران المصابة بالاسكارس ، تسعون فأرا استخدمت في هذه الدراسة قسمت الي سبع مجموعات ، استخدمت المجموعة الاولي والثانية كمجوعات ضابطة والمجموعات 3 ، 4،5،6 عوملت باستخدام مستخلص نبات الثوم (الالسين) عند جرعات 0.1 و 0.2و 0.3و 0.4 ملي جرام لكل جرام من وزن الجسم علي التوالي لمدة اربعة اسابيع مرتين اسبوعياً .
المجموعة السابعة عوملت باستخدام عقار سترات الببرازين عند جرعة 10 ملي جرام لكل كيلو جرام من وزن الجسم لمدة اربعة اسابيع مرتين اسبوعياً. كل المجموعات ذبحت بعد 30 يوما . تم فحص الجهاز المناعي مع الاستجابات المناعية للسيتوكينات والانترلوكين -10 و تي – ان – اف – الفا متزامنة مع قياسات وظائف الكبد وقياس مستوي المانوالدهيد كعامل مناعي مساعد . اظهرت نتائج هذه الدراسة زيادة معنوية عالية في معدلات(الانترلوكين -10) وايضا في معدلات (تي – ان – اف – الفا) في المجموعات التي عوملت بالمستخلص النباتي وايضا اظهرت الدراسة انخفاضا معنويا في معدلات المانوالدهيد في المجموعات التي عوملت بالمستخلص النباتي مع زيادة معنوية في المجموعة التي عوملت بسترات الببرازين ، من ناحية اخري اظهرت النتائج زيادة معنوية في وظائف الكبد للمجموعة التي عوملت بعقار سترات الببرازين مع حدوث تحسن في وظائف الكبد بالنسبة للمجموعات التي عوملت باستخدام المستخلص النباتي.